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Safety and feasibility of preoperative exercise training during neoadjuvant treatment before surgery for adenocarcinoma of the gastro-oesophageal junction

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Background: **Neoadjuvant chemotherapy or chemoradiotherapy is used widely before tumour resection in cancer of the gastro-oesophageal junction (GOJ). Strategies to improve treatment tolerability are warranted. This study examined the safety and feasibility of preoperative exercise training during neoadjuvant treatment in these patients.**

Methods: **Patients were allocated to a standard-care control group or an exercise group, who were prescribed standard care plus twice-weekly high-intensity aerobic exercise and resistance training sessions. The primary endpoint was the incidence of serious adverse events (SAEs) that prevented surgery, including death, disease progression or physical deterioration. Preoperative hospital admission, postoperative complications, changes in patient-reported quality of life and pathological treatment response were also recorded. In the exercise group, adherence to exercise and changes in aerobic fitness, muscle strength and body composition were measured.**

Results: **The incidence of SAEs was not increased in the exercise group. The risk of failure to reach surgery was 5 *versus* 21 per cent in the control group (risk ratio (RR) 0·23, 95 per cent c.i. 0·04 to 1·29), the risk of preoperative hospital admission was 15 *versus* 38 per cent respectively (RR 0·39, 0·12 to 1·23) and the risk of postoperative complications was 58 *versus* 57 per cent (RR 1·06, 0·61 to 1·73). The exercise group attended a mean of 17·5 sessions, and improved fitness, muscle strength and Functional Assessment of Cancer Therapy – Esophageal (FACT-E) total score compared with the baseline level.**

Conclusion: **Preoperative exercise training during neoadjuvant treatment in patients with GOJ cancer is safe and feasible, with improvements in fitness, strength and quality of life. Preoperative exercise training may be associated with a lower risk of critical SAEs that preclude surgery or result in hospitalization.**

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Introduction

Adenocarcinoma of the gastro-oesophageal junction (GOJ) is a growing challenge, with an increasing incidence rate and poor prognosis[1,2]. For many patients, surgical removal of the primary tumour is an essential component of treatment with intent to cure[3,4]. Neoadjuvant chemotherapy or chemoradiotherapy is used widely in patients with locally advanced or node-positive tumours to achieve clear resection margins and improve long-term survival[5,6]. Although neoadjuvant treatments have improved long-term survival, these approaches are not without challenges. In non-responders, there is a risk of disease progression, and physical deterioration and other toxicities can increase the risk of serious postoperative complications or prevent planned surgery due to poor performance status. It remains a challenge to ensure that patients with operable GOJ cancer reach surgery in good physiological condition[7].

Although neoadjuvant treatment can result in adverse reactions, it also provides a preoperative window to counteract physiological decline and improve the condition of these patients before surgery. Preoperative exercise training has been shown to reduce the risk of complications by up to 50 per cent in patients undergoing gastrointestinal surgery[8]. The role of preoperative exercise remains poorly investigated, however, with regard to tolerability of neoadjuvant therapies that can have a profound impact on exercise capacity, participation and adaptive responses[9].

The present study explored the safety and feasibility of high-intensity aerobic and resistance exercise during neoadjuvant treatment in patients with GOJ cancer. The primary objective was to examine the rates of serious adverse events (SAEs). These SAEs included issues that precluded surgery (death, disease progression or severe physical deterioration). Preoperative hospital admission, need for dose reduction or postponement, and specific toxicities related to neoadjuvant treatment, and postoperative complications were also recorded. Adherence to the exercise prescription, involving attendance rate, number of interruptions and exercise modifications, and changes in aerobic fitness, muscle function and body composition were also determined. It was hypothesized that preoperative exercise training would be safe (would not increase the risk of SAEs compared with standard care) and feasible, resulting in improved cardiopulmonary and muscular fitness levels.

Methods

This was a prospective, controlled, feasibility study based at Rigshospitalet, Copenhagen University Hospital. Patients with histologically verified, resectable adenocarcinoma of the GOJ were eligible for inclusion. Major exclusion criteria were: age below 18 or more than 80 years; inoperability based on imaging; pregnancy; presence of any other known malignancy requiring active treatment; ineligibility for neoadjuvant treatment; WHO performance status greater than 1; physical or mental disabilities precluding physical testing and/or exercise; and inability to read and understand Danish. The study was approved by the local ethics committee (H-17003961) and registered with Clinicaltrials.gov (NCT02722785).

Patients were recruited from the Department of Surgical Gastroenterology, Rigshospitalet, a large-volume centre responsible for treatment of operable GOJ cancer for the whole of Eastern Denmark. Eligible patients were informed of the study during their first visit to the outpatient clinic following a multidisciplinary medical conference, and provided signed informed consent before any study-related procedures were performed.

Standard gastro-oesophageal junction cancer treatment

All eligible subjects were scheduled to receive standard of care at Rigshospitalet. This consisted of three neoadjuvant cycles of chemotherapy at intervals of 3 weeks followed by surgery and three further cycles of adjuvant chemotherapy. Each cycle of chemotherapy consisted of epirubicin (Pharmachemie, Haarlem, the Netherlands) 50 mg/m^2 intravenously on day 1, capecitabine (Accord Healthcare, Harrow, UK) 500 mg/m^2 orally twice daily for 21 days and either cisplatin (Hospira UK, Hurley, UK) 60 mg/m^2 intravenously (ECX) or oxaliplatin (Fresenius Kabi Oncology, Bordon, UK) 130 mg/m^2 on day 1 (EOX)[10]. Owing to participation in another RCT, some patients received treatment according to the CROSS regimen[11], involving five cycles of paclitaxel (Fresenius Kabi Oncology) 50 mg/m^2 and carboplatin (Fresenius Kabi Oncology) intravenously in doses titrated to achieve an area under the curve of 2 mg per ml per min given once a week concurrently with radiotherapy, 41·4 Gy in 23 fractions, 5 days per week.

Surgery was performed 4–6 weeks after the completion of neoadjuvant therapy. The Ivor Lewis procedure was used consistently throughout the study, performed either as robot-assisted minimally invasive oesophagectomy, hybrid (robot-assisted laparoscopy combined with thoracotomy) or open (laparotomy and thoracotomy), as described previously[12].

Group allocation

Participants were enrolled to one of two study arms without randomization, based on their geographical residential location; subjects residing within a predefined area of the Greater Copenhagen region were allocated to the exercise group and those residing outside this area were allocated to a standard-care control group. All subjects who agreed to participate performed a series of baseline tests during an outpatient clinic visit. This included evaluation of lower-body physical function by the 30-s sit-to-stand test and of upper-body physical function by handgrip strength using a hand-held dynamometer. Body composition was measured by bioelectrical impedance analysis using a Bioelectrical Impedance Analyzer (MC-780 MA; Tanita, Tokyo, Japan). The skeletal muscle index (SMI), defined as total cross-sectional transverse muscle area (cm^2 at the L3 region normalized to height; cm^2/m^2), was measured on available CT scans using OsiriX (v 3.5.1, 32-bit; http://www.osirix-viewer.com)[13].

Participants residing outside the predefined area of Greater Copenhagen, enrolled in the usual-care control group, had to travel for at least 45 min (up to 2 h) to reach the hospital; this was considered unfeasible for participation in a hospital-based training programme. These patients followed the standard of care delivered by the Departments of Oncology and Surgical Gastroenterology, which included information regarding smoking cessation, diet, alcohol and physical activity guidelines through consultations with clinical dieticians and nurse specialists. Those in the control group were allowed to participate in any standard hospital or municipality-based exercise programmes.

Participants residing within the Greater Copenhagen area were allocated to supervised training intervention at the Centre for Physical Activity Research, Rigshospitalet. The training programme consisted of supervised high-intensity aerobic and resistance exercise with twice-weekly sessions of approximately 75 min (*Fig. S1*, supporting information). Individual fitness and strength capacity were used to personalize the programme. Each session included a 10-min warm-up on a stationary bicycle followed by 21–28 min of high-intensity interval training consisting of 4 × 4 min with 3 min of low-intensity active recovery between each high-intensity bout. Resistance training comprised four exercises for the major muscle groups: chest press, leg press, lateral pull and knee extension, with one warm-up set followed by three sets of 8–12 repetitions. Each session was supervised by a trained instructor to ensure proper technique, and progression in training load.

Assessments and study endpoints

The primary outcome measure was the frequency of SAEs, defined as events that prevented surgery: death, verified disease progression due to the development of distant metastasis or local tumour invasion to nearby structures preventing radical tumour resection, or severe physical deterioration following neoadjuvant treatment, leading to a joint decision between patient and surgeon (not involved in the study) that the patient was unfit for oesophagectomy. Secondary endpoints included assessment of neoadjuvant treatment tolerability involving: non-scheduled preoperative hospitalization (for more than 24 h), dose reduction, postponement of scheduled neoadjuvant treatment, and incidence of grade 1–4 toxicities according to Common Toxicity Criteria (CTC). Postoperative complications were graded according to the Clavien–Dindo classification[14]; ‘all complications’ were defined as Clavien–Dindo grade II or above, and ‘serious complications’ as Clavien–Dindo grade III or above. A comprehensive complication index (CCI) score was calculated as described previously[15] and postoperative duration of hospital stay was determined.

Patient-reported tolerability to neoadjuvant treatment was assessed by changes in health-related quality of life from baseline to the day before scheduled surgery using the Functional Assessment of Cancer Therapy – Esophageal (FACT-E) questionnaire[16].

Response to treatment was measured by infiltration of the resection margin (R0, R1, R2)[17] and analysis of resected tumours for intratumoral T-cell densities (immunoscore), tumour regression grade and pathological tumour stage (pTNM) as described previously by Mandard and colleagues[18].

Feasibility and efficacy of preoperative exercise training

Feasibility of exercise training was assessed by adherence to the prescribed programme, including registration of the following metrics: attendance rate, occurrence of exercise modification (dose reduction or early termination of individual sessions), training interruption and permanent discontinuation[19]. The number of attended sessions was recorded for each participant and the adherence rate was determined as the number of planned sessions attended. Exercise dose modification was defined as the number of sessions with a reduction in volume or intensity from the prescribed session, as well as instances of early termination before the full programme had been performed. Training interruption was defined as a period of 7 days or more without a training session. Permanent discontinuation was noted if participants withdrew entirely from the exercise programme, regardless of whether they remained in the study.

For every session, an instructor was present to supervise the exercise programme. Participants were asked about common adverse reactions (fatigue, nausea, pain and dizziness) before the start of every session, and after each session any notable changes (improvement, unchanged or worsening) were recorded.

Participants in the exercise group were evaluated for changes in cardiopulmonary fitness, muscle strength and

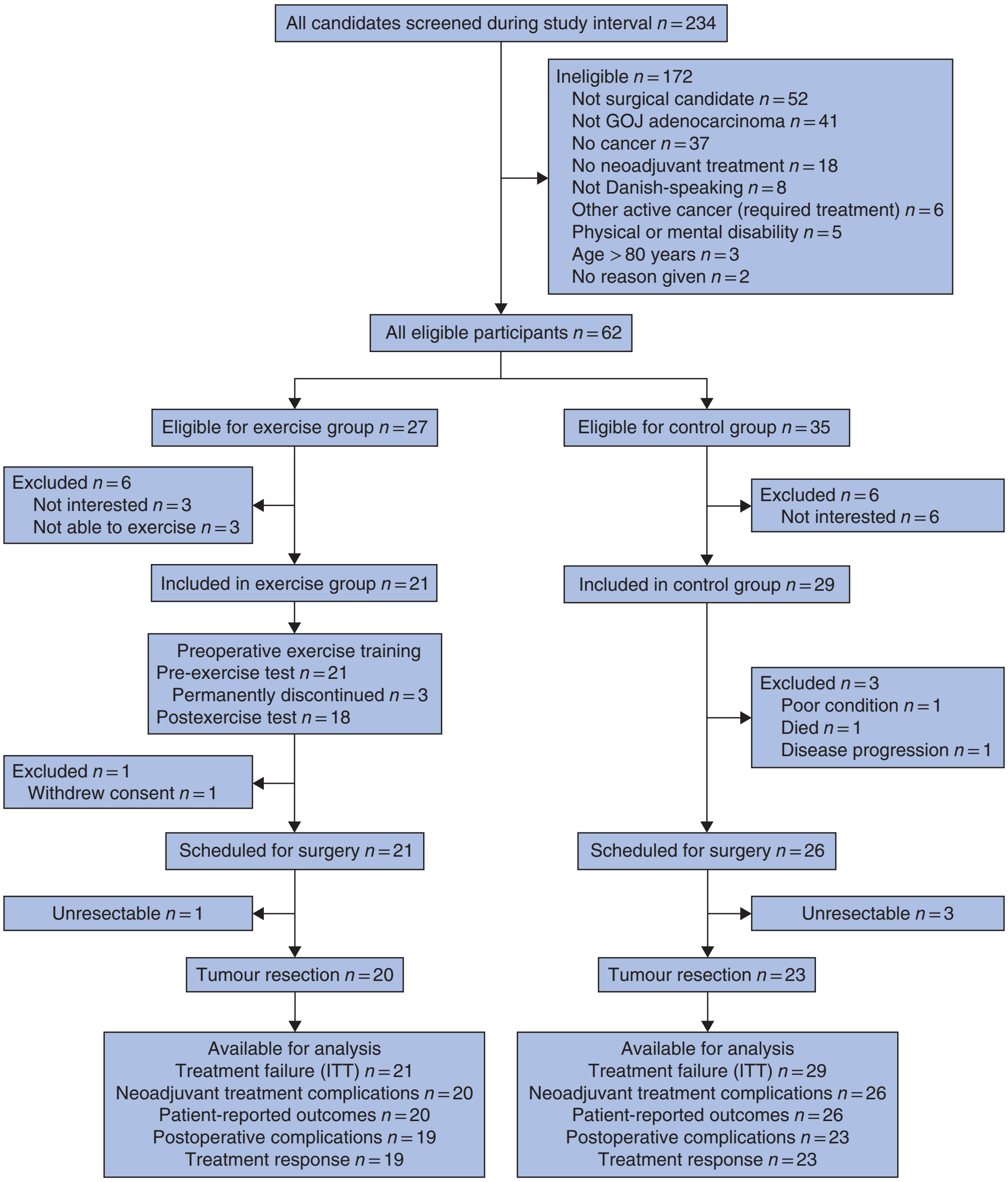

Fig. 1 Flowchart for the study, based on intention-to-treat (ITT) numbers. One participant in the exercise group who received the scheduled treatment withdrew consent, and therefore no data are available for treatment complications or response. GOJ, gastro-oesophageal junction

body composition before and after the intervention. Fat mass, bone mass, fat-free mass and bone mineral density were analysed by whole-body dual-energy X-ray absorptiometry (DEXA) (DPX-IQ; Lunar Corporation, Madison, Wisconsin, USA)[20]. Muscle strength was evaluated by the one-repetition maximum (1RM) test in resistance training machines (Technogym Runrace, Gambettola, Italy). Participants were positioned correctly in the machine and performed eight repetitions on a light load. After a short rest, progressively higher loads were added and the participant performed one repetition on each load. The procedure was repeated until the single repetition could not be completed with proper technique. The load of the last successful repetition was noted as the test score. Fitness was assessed using the $Watt_{max}$ test on an electronically braked bicycle ergometer (Monark Ergomedic 839E Bicycle; Monark, Varberg, Sweden). Participants performed a 3-min warm-up on a workload of 50 W, and then undertook a graded $Watt_{max}$ test with a 20-W incremental load added every minute until exhaustion.

Table 1 Participant characteristics

	All participants ($n = 50$)	Exercise group ($n = 21$)	Control group ($n = 29$)	*P*
Age (years)*	64·8(7·7)	63·9(8·2)	65·5(7·3)	0·464
Sex ratio (M : F)	45 : 5	18 : 3	27 : 2	0·638
BMI (kg/m^2)*	28·1(5·5)	28·4(5·6)	27·8(5·5)	0·717
Diabetes	9 (18)	5 (24)	4 (14)	0·464
Cardiovascular disease	6 (12)	3 (14)	3 (10)	0·686
ASA grade				
0	4 (8)	3 (14)	1 (3)	0·211
I	12 (24)	7 (33)	5 (17)	
II	26 (52)	8 (38)	18 (62)	
III	8 (16)	3 (14)	5 (17)	
Smoker				
Current	10 (20)	1 (5)	9 (31)	0·041
Previous	29 (58)	16 (76)	13 (45)	
Never	11 (22)	4 (19)	7 (24)	
Alcohol intake (units/week)†				
≤ 7 or ≤ 14	42 (84)	19 (90)	23 (79)	0·441
> 7 or > 14	8 (16)	2 (10)	6 (21)	
Physical activity level (min MVPA/week)				
< 150	38 (76)	17 (81)	21 (72)	0·526
≥ 150	12 (24)	4 (19)	8 (28)	
cTNM stage				
I	5 (10)	2 (10)	3 (10)	0·691
II	30 (60)	14 (67)	16 (55)	
III	15 (30)	5 (24)	10 (34)	
Physical function*				
Sit-to-stand performance (repetitions)	13·2(3·8)	13·9(3·6)	12·7(3·9)	0·298
Hand-grip strength (kg)	41·1(9·9)	39·8(7·6)	42·0(11·4)	0·456
Body composition (bioelectrical impedance analyses)*				
Lean body mass (kg)	62·8(9·9)	62·1(10·6)	63·2(9·6)	0·740
Fat percentage (%)	25·3(8·6)	26·0(8·7)	25·7(8·7)	0·605
Skeletal muscle index (cm^2/m^2)*	53·7(8·8)	52·8(9·2)	54·2(8·6)	0·589
Neoadjuvant treatment‡	*n* = 46	*n* = 20	*n* = 26	
ECX	18 (39)	8 (40)	10 (38)	0·864
EOX	22 (48)	10 (50)	12 (46)	
CROSS	6 (13)	2 (10)	4 (15)	
Surgical procedure§	*n* = 42	*n* = 19	*n* = 23	
RAMIE	2 (5)	0 (0)	2 (9)	0·227
Hybrid (laparoscopy, thoracotomy)	7 (17)	2 (11)	5 (22)	
Open (Ivor Lewis)	33 (79)	17 (89)	16 (70)	

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †Presented as adherence to the Danish national guidelines of 7 units or less for women and 14 units or less for men per week. ‡Four subjects not included owing to exclusion/withdrawal before or during neoadjuvant treatment; §eight subjects not included owing to exclusion/withdrawal and no surgery performed. MVPA, moderate to vigorous physical activity; ECX, epirubicin + cisplatin + capecitabine; EOX, epirubicin + oxaliplatin + capecitabine; CROSS, paclitaxel + carboplatin + radiotherapy; RAMIE, robot-assisted minimally invasive oesophagostomy.

Participants' peak performance ($Watt_{max}$) was applied to estimate cardiopulmonary fitness level, peak oxygen consumption ($\dot{V}O_{2peak}$, ml oxygen per min per kg) using the standard formula proposed by the American College of Sports Medicine, for metabolic equations[21].

Statistical analysis

The feasibility study aimed to include a minimum of 20 subjects in each of the two arms without a power calculation. Baseline comparison between the two arms was performed using Student's unpaired *t* test for continuous variables and the χ^2 test for categorical variables. Treatment tolerability variables are presented as absolute risk for each group, and explorative analyses of the between-group risk ratio with 95 per cent confidence intervals were calculated using χ^2 or Fisher's exact test. Patient-reported outcomes (FACT-E scores) were analysed for in-group changes with 95 per cent confidence intervals from baseline to surgery using Student's paired *t* test, and between-group differences for change scores were estimated with Student's unpaired *t* test.

For the exercise group, adherence to the exercise programme was determined by mean attendance rate, and

Table 2 Treatment tolerability

	All participants (*n* = 50)	Exercise group (*n* = 21)	Control group (*n* = 29)	Risk ratio*
Treatment failure (intention to treat)				
No. of patients precluded from surgery	7 (14)	1 (5)	6 (21)	0·23 (0·04, 1·29)
No. of deaths	1	0	1	–
Disease progression	5	1	4	–
Deconditioning	1	0	1	–
Complications of neoadjuvant treatment	*n* = 46	*n* = 20	*n* = 26	
Preoperative hospitalization	13 (28)	3 (15%)	10 (38)	0·39 (0·12, 1·23)
Total days	78	29	49	–
Treatment dose reduction	15 (33)	6 (30)	9 (35)	0·87 (0·40, 2·03)
Treatment postponed	12 (26)	6 (30)	6 (23)	1·30 (0·49, 3·42)
Total events	14	7	7	–
CTC toxicity grade	11 (24)	3 (15)	8 (31)	0·45 (0·14, 1·47)
1–2	10	2	8	–
3–4	1	1	0	–
Postoperative complications	*n* = 42	*n* = 19	*n* = 23	
All complications‡	24 (57)	11 (58)	13 (57)	1·02 (0·61, 1·73)
Serious complications§	9	4	5	–
Anastomotic leak	3	1	2	–
Pneumonia	7	4	3	–
CCI score†	20·9 (0–47·3)	20·9 (0–33·5)	20·9 (0–26·2)	–
Postoperative duration of hospital stay (days)†	9 (8·5–11)	10 (9–11)	9 (8–11)	–

Values in parentheses are percentages unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals. †Values are median (i.q.r.). ‡Defined as events with Clavien–Dindo grade II or above; §defined as events with Clavien–Dindo grade II or above. CTC, Common Toxicity Criteria; CCI, comprehensive complication index.

Table 3 Patient-reported outcomes

	Change in score from baseline to surgery			
	All participants (*n* = 46)	Exercise group (*n* = 20)	Control group (*n* = 26)	Mean difference
Physical wellbeing	−0·4 (−1·8, 4·5)	1·2 (−0·9, 3·2)	−1·6 (−3·5, 0·2)	2·8 (0·1, 5·5)
Social wellbeing	0·0 (−0·9, 1·0)	0·0 (−1·5, 1·5)	0·0 (−1·3, 1·5)	0·0 (−2·1, 2·0)
Emotional wellbeing	1·8 (0·7, 2·9)	3·0 (1·1, 4·9)	0·9 (−0·3, 2·1)	2·1 (−0·6, 4·2)
Functional wellbeing	−0·1 (−1·8, 1·6)	−0·4 (−3·6, 2·8)	0·2 (−1·7, 2·0)	−0·6 (−4·0, 2·8)
Oesophageal cancer subscale	5·1 (1·5, 8·7)	8·8 (3·8, 13·9)	2·3 (−2·7, 7·2)	6·6 (−0·4, 13·6)
FACT-E trial outcome index	4·6 (−0·9, 10·1)	9·6 (1·0, 18·1)	0·8 (−6·6, 8·2)	8·8 (−2·1, 19·8)
FACT-G total	1·3 (−2·6, 5·3)	3·7 (−3·3, 10·8)	−0·5 (−5·3, 4·2)	4·3 (−3·7, 12·2)
FACT-E total	6·4 (−0·1, 13·0)	12·6 (2·7, 22·9)	1·8 (−6·9, 10·4)	10·8 (−2·1, 23·8)

Values are mean (95 per cent c.i.). FACT-E/G, Functional Assessment of Cancer Therapy – Esophageal/General.

the absolute risk (at least 1 case) of exercise interruption and dose modification. In-group changes in aerobic fitness, muscle strength and body composition from before to after the intervention were calculated with 95 per cent confidence intervals using Student's paired *t* test.

Results

Between 1 April 2016 and 1 May 2017, 237 potential candidates were screened for eligibility. Owing to an uneven recruitment rate, subjects were enrolled in both arms until a minimum of 20 subjects had been included in each arm. Sixty-two candidates were eligible for inclusion, 27 in the exercise group and 35 in the control group. Of these, 21 (78 per cent) were included in the exercise group and 29 (83 per cent) in the control group (*Fig. 1*). The mean(s.d.) age of participants was 64·8(7·7) years, their BMI was 28·1(5·5) kg/m^2, and 90 per cent were men. There was a higher proportion of smokers in the control group than in the exercise group ($P = 0{\cdot}041$), but no significant differences in scheduled neoadjuvant treatments or surgical procedures (*Table 1*).

Treatment tolerability and response

Data for treatment tolerability are presented in *Table 2*. The risk of treatment failure in the exercise group was 5

Fig. 2 Schematic overview of adherence to exercise, showing individual exercise attendance, interruptions and modifications for each subject in the exercise group, including the timing of concurrent neoadjuvant treatment

per cent, compared with 21 per cent in the control group (risk ratio (RR) 0·23, 95 per cent c.i. 0·04 to 1·29). During neoadjuvant treatment, the risk of hospital admission was 15 and 38 per cent respectively (RR 0·39, 0·12 to 1·23). The rate of reduction in neoadjuvant treatment dosage was 30 per cent in the exercise group *versus* 35 per cent in the control group (RR 0·87, 0·40 to 2·03), and the rate of treatment postponement was 30 and 23 per cent respectively (RR 1·30, 0·49 to 3·42). The risk of presenting with CTC grade 1–4 toxicity was 15 per cent in the exercise group and 31 per cent in the control group (RR 0·45, 0·14 to 1·47).

The risk for all postoperative complications was 58 per cent in the exercise group compared with 57 per cent in the control group (RR 1·06, 95 per cent c.i. 0·61 to 1·73). The median postoperative duration of hospital stay was 10 days in the exercise group *versus* 9 days in the control group. There were three anastomotic leaks overall (1 in the exercise group and 2 in the control group), and seven patients developed pneumonia (4 and 3 patients respectively). The median CCI score was 20·9 (i.q.r. 0–47·3).

Data for treatment response, including surgical clearance rate (R0), tumour immunoscore, tumour regression grade and pTNM stage, are presented in *Table S1* (supporting information).

From baseline to surgery, participants in the exercise group reported significant improvements in the emotional wellbeing subscale (+3·0, 95 per cent c.i. 1·1 to 4·9) and the oesophageal cancer subscale (+8·8, 3·8 to 13·9) of the FACT-E questionnaire. In addition, the FACT-E trial outcome index score (+9·6, 1·0 to 18·1) and FACT-E total score (+12·6, 2·7 to 22·9) improved in the exercise group. No changes were observed in the control group for patient-reported outcomes (*Table 3*) and only the change in physical wellbeing differed significantly between the groups (mean difference 2·8, 0·1 to 5·5).

Feasibility of preoperative exercise training

Data for adherence to preoperative exercise training are shown in *Fig. 2*. Participants in the exercise group

Table 4 Efficacy of exercise training

Physiological endpoints	Before exercise*	After exercise*	Mean difference†
Fitness			
Peak power (W)	153·2(63·5)	165·2(52·1)	+12 (0·1, 24·0)
$V\text{O}_{2\text{peak}}$ (ml per min per kg)	25·23(8·38)	26·62(6·78)	+1·39 (0·03, 2·74)
Muscle strength, 1RM			
Leg press (kg)	116·4(27·8)	143·9(30·3)	+26·9 (17·6, 36·3)
Knee extension (kg)	50·1(10·8)	60·4(13·1)	+9·9 (6·2, 13·7)
Chest press (kg)	31·3(9·7)	36·8(12·8)	+5·1 (2·7, 7·6)
Row (kg)	59·2(14·3)	68·9(16·5)	+8·9 (5·4, 12·4)
Body composition, dual-energy X-ray absorptiometry scan			
Lean body mass (kg)	55·6(10·4)	57·0(10·7)	−0·1 (−1·0, 0·8)
Fat mass (kg)	29·6(13·4)	32·0(12·5)	−0·3 (−1·8, 3·1)
Fat percentage (%)	33·6(9·3)	35·1(7·6)	−0·4 (−1·8, 0·9)

Values are mean(s.d.); †values in parentheses are 95 per cent confidence intervals. $V\text{O}_{2\text{peak}}$, peak oxygen consumption; 1RM, 1-repetition maximum.

had a mean(s.d.) attendance of 17·5(8·7) sessions, corresponding to 68·7 per cent of the prescribed programme, and three of the 21 participants permanently discontinued the programme. Overall, participants were able to follow the exercise prescription regarding volume and progression for exercise intensity (*Table S2*, supporting information), although 94 of the total 365 sessions (25·8 per cent) required dose reduction (85 sessions) or early termination (9 sessions) compared with the programme prescribed for that session (*Table S3*, supporting information).

During the preoperative period, a high prevalence of self-reported symptoms was recorded before the exercise sessions, including fatigue (21 patients; 148 sessions (42·9 per cent)), nausea (14 patients; 84 sessions (23·4 per cent)), pain (16 patients; 112 sessions (32·5 per cent)) and dizziness (13 patients; 58 sessions (16·8 per cent)). Participants reported worsening of these pre-exercise symptoms in 0·9–3·5 per cent of all sessions, with reported improvement in symptom burden in 3·8–14·2 per cent of the sessions after acute exercise (*Table S3*, supporting information).

Changes in physiological endpoints from before to after the intervention are presented in *Table 4*. There were significant improvements in: peak power (+12 (95 per cent c.i. 0·1 to 24) W), corresponding to a + 1·39 (0·03 to 2·74) ml oxygen per kg per min improvement in estimated $V\text{O}_{2\text{peak}}$; muscle strength for leg press (+26·9 (17·6 to 36·3) kg); knee extension (+9·9 (6·2 to 13·7) kg); chest press (+5·1 (2·7 to 7·6) kg) and seated row (+8·9 (5·4 to 12·4) kg). There were no changes in body composition.

Discussion

The principal finding of this study is that high-intensity exercise training performed during neoadjuvant treatment was safe and feasible and led to improved aerobic fitness, strength and health-related quality of life. Preoperative exercise may be associated with a lower risk of treatment failure and preoperative hospital admission during neoadjuvant treatment, which could have important implications for future perioperative management of patients with GOJ cancer[22,23].

Over the past decade, physical exercise has been explored extensively to improve symptom control through better physical capacity and psychosocial wellbeing in the oncology setting. During the same period, preclinical studies have reported that exercise may be associated with direct anticancer mechanisms and the capacity to modulate therapeutic efficacy of traditional treatment regimens[24–26]. Few clinical studies have, however, reported treatment-related endpoints including measures of treatment tolerability and response. The present study demonstrated considerable reduction in the risk of treatment failure in the exercise group compared with the control group (5 *versus* 21 per cent respectively). This is arguably the single most important outcome for patients undergoing neoadjuvant treatment, as the chances of long-term survival fall significantly, from a 5-year relative survival rate of 20–40 per cent in operable patients to less than 5 per cent in inoperable patients[27].

Satisfactory tolerability to neoadjuvant treatment is critical in patients with GOJ cancer in order to justify the delay before surgery. It was necessary, therefore, to determine whether participation in exercise training would increase the risk of SAEs during the preoperative period. In fact, the risk of preoperative hospital admission in the exercise group (15 *versus* 38 per cent in the control group) and registered CTC toxicity (15 *versus* 31 per cent respectively) were halved relative to values in the control group. Improvement in several domains of the FACT-E questionnaire in the exercise group emphasized that exercise participation is safe, and possibly beneficial, with regard to treatment tolerability.

If preoperative exercise does improve treatment tolerability, this may translate into improved tumour response in the preoperative period. Recent experimental studies[25,26] have shown that exercise can induce a synergistic anticancer effect when administered in conjunction with regular therapies. A 6-week programme of preoperative aerobic exercise during neoadjuvant radiotherapy was associated with a greater likelihood of response to radiotherapy in patients with rectal cancer[28]. Although the present study was probably too small to reveal any differences in response as evaluated by tumour regression grade and pTNM stage, these other observations indicate that exercise may augment the response to chemotherapy and/or radiotherapy. This might be related to improved intratumoral blood perfusion with reductions in hypoxia, changes in tumour metabolism, enhancement of the immunogenic profile and inhibition of the metastatic process[9]. A few clinical trials have reported prognostic data to elucidate whether such additive and/or synergetic anticancer effects can be accomplished in patients with cancer. In the START trial, Courneya and colleagues[29] found that women with early-stage breast cancer who performed resistance training had higher chemotherapy completion rates compared with controls receiving usual care. The same authors found that participation in aerobic or resistance training was associated with a non-significant 40 per cent reduction in the recurrence-free interval (RFI). Subgroup analyses revealed that the exercise-induced improvement in RFI was confined to patients who had received more than 85 per cent of planned dosage, with no apparent effect in patients receiving less than this dose[30].

Establishing adherence and efficacy of a structured, high-intensity exercise programme during chemotherapy or chemoradiotherapy was an important secondary objective in the present study. A recent study[31] reported an average loss of 5 kg lean body mass in patients with oesophageal cancer undergoing neoadjuvant treatment, tripling the number of patients with sarcopenia, an independent predictor of postoperative complication risk[32] and poor long-term prognosis[33]. Maintained lean body mass, combined with improvements in fitness and muscle strength, in the exercise group are important findings in the present study. Overall, the exercise group followed the prescribed programme with regard to attendance, dose and intensity, but relatively high rates of modification and interruption were needed. This suggests that patients with coexisting morbidities undergoing symptom-heavy therapies require close monitoring and individualization of the programme in order to optimize exercise participation and output. Patient-reported fatigue, pain, nausea and dizziness before and after each training session did not seem to indicate that patient-reported symptoms hampered participation in exercise.

Recently, preoperative exercise interventions have gained momentum in the context of prehabilitation[34], but consensus is lacking regarding the overall aim, content and organizational setup of such programmes. A recent Cochrane review[35] showed that preoperative exercise training can lower risk of pulmonary complications in patients with non-small cell lung cancer, and personalized prehabilitation with aerobic exercise was found to lower complication risk by 50 per cent after major gastrointestinal surgery[8]. In the present study, postoperative complication risk was no different in the exercise group compared with controls, despite improvements in physiological performance. This may reflect the small numbers of patients and relatively few serious complications in both groups, including anastomotic leakage (3 patients) and pneumonia (7 patients). The imbalance in presurgical dropouts (1 in the exercise group *versus* 6 in the control group) may also have influenced postoperative outcomes, as a larger proportion of potentially high-risk patients did not undergo surgery in the control group.

The present study has important limitations. Most notably, it has a limited sample size and non-randomized design, which was chosen to improve accrual rates while still enabling a non-exercise group to be used as reference before potentially launching a large-scale randomized trial. The findings of the present study should therefore be interpreted with care, given the multitude of factors influencing treatment tolerability, particularly from a non-randomized feasibility study. There may have been systematic differences between the two study arms, given the pragmatic decision to use a non-randomized parallel-group design including subjects from rural and urban areas for the two arms. This may have led to socioeconomic differences, as there was a higher proportion of smokers in the control (rural) group. The inclusion only of patients with GOJ adenocarcinoma limits the generalizability of the results. The decision not to include other oesophageal carcinomas was made mainly for logistical reasons, but also to minimize the already large number of confounding variables within an explorative pilot study. The control group received no face-to-face attention, and the potential psychosocial effects of interacting with health professionals/trainers cannot be separated from the direct exercise effects.

Although the findings of the present study should be considered preliminary, preoperative exercise training should be examined with the objective of improving treatment tolerability and lowering the risk of treatment failure in patients with GOJ cancer in a definitive RCT.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.